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Guidelines for Carcinogen Risk Assessment

Section 1.3
Key Features of the Cancer Guidelines

Risk Assessment Forum
U.S. Environmental Protection Agency
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options would only be used to address uncertainties or the absence of critical data. Default options are inferences based on general scientific knowledge of the phenomena in question and are also matters of policy concerning the appropriate way to bridge uncertainties that concern potential risk to human health.

These cancer guidelines do not suggest that all of the kinds of data covered here will need to be available or used for either assessment or decision making. The level of detail of an assessment is a matter of Agency management discretion regarding applicable decision-making needs. The Agency generally presumes that key cancer information (e.g., assessments contained in the Agency's Integrated risk Information System) is "influential information" as defined by the EPA Information Quality Guidelines and "highly influential" as defined by OMB's Information Quality Bulletin for Peer Review (OMB 2004).

1.3. KEY FEATURES OF THE CANCER GUIDELINES

1.3.1. Critical Analysis of Available Information as the Starting Point for Evaluation

As an increasing understanding of carcinogenesis is becoming available, these cancer guidelines adopt a view of default options that is consistent with EPA's mission to protect human health while adhering to the tenets of sound science. Rather than viewing default options as the starting point from which departures may be justified by new scientific information, these cancer guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information. Preference is given to using information that has been peer reviewed, e.g., reported in peer-reviewed scientific journals. The primary goal of EPA actions is protection of human health; accordingly, as an Agency policy, risk assessment procedures, including default options that are used in the absence of scientific data to the contrary, should be health protective (U.S. EPA, 1999b).

Use of health protective risk assessment procedures as described in these cancer guidelines means that estimates, while uncertain, are more likely to overstate than understate hazard and/or risk. NRC (1994) reaffirmed the use of default options as "a reasonable way to cope with uncertainty about the choice of appropriate models or theory" (p. 104). NRC saw the

need to treat uncertainty in a predictable way that is "scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decision-makers" (p. 86). The extent of health protection provided to the public ultimately depends upon what risk managers decide is the appropriate course of regulatory action. When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision.

Encouraging risk assessors to be receptive to new scientific information, NRC discussed the need for departures from default options when a "sufficient showing" is made. It called on EPA to articulate clearly its criteria for a departure so that decisions to depart from default options would be "scientifically credible and receive public acceptance" (p. 91). It was concerned that *ad hoc* departures would undercut the scientific credibility of a risk assessment. NRC envisioned that principles for choosing and departing from default options would balance several objectives, including "protecting the public health, ensuring scientific validity, minimizing serious errors in estimating risks, maximizing incentives for research, creating an orderly and predictable process, and fostering openness and trustworthiness" (p. 81).

Appendices N-1 and N-2 of NRC (1994) discussed two competing standards for choosing default options articulated by members of the committee. One suggested approach would evaluate a departure in terms of whether "it is scientifically plausible" and whether it "tends to protect public health in the face of scientific uncertainty" (p. 601). An alternative approach "emphasizes scientific plausibility with regard to the use of alternative models" (p. 631). Reaching no consensus on a single approach, NRC recognized that developing criteria for departures is an EPA policy matter.

The basis for invoking a default option depends on the circumstances. Generally, if a gap in basic understanding exists or if agent-specific information is missing, a default option may be used. If agent-specific information is present but critical analysis reveals inadequacies, a default

option may also be used. If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager. In this case, the default model not only fits the data, but also serves as a benchmark for comparison with other analyses. This case also highlights the importance of extensive experimentation to support a conclusion about mode of action, including addressing the issue of whether alternative modes of action are also plausible. Section 2.4 provides a framework for critical analysis of mode of action information to address the extent to which the available information supports the hypothesized mode of action, whether alternative modes of action are also plausible, and whether there is confidence that the same inferences can be extended to populations and lifestages that are not represented among the experimental data.

Generally, cancer risk decisions strive to be "scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decision-makers" (NRC, 1994). Scientific defensibility would be evaluated through use of EPA's Science Advisory Board, EPA's Office of Pesticide Programs' Scientific Advisory Panel, or other independent expert peer review panels to determine whether a consensus among scientific experts exists. Consistency with the Agency's statutory mission would consider whether the risk assessment overall supports EPA's mission to protect human health and safeguard the natural environment. Responsiveness to the needs of decisionmakers would take into account pragmatic considerations such as the nature of the decision; the required depth of analysis; the utility, time, and cost of generating new scientific data; and the time, personnel, and resources allotted to the risk assessment.

With a multitude of types of data, analyses, and risk assessments, as well as the diversity of needs of decisionmakers, it is neither possible nor desirable to specify step-by-step criteria for decisions to invoke a default option. A discussion of major default options appears in the Appendix. Screening-level assessments may more readily use default parameters, even worst-case assumptions, that would not be appropriate in a full-scale assessment. On the other hand, significant risk management decisions will often benefit from a more comprehensive assessment, including alternative risk models having significant biological support. To the extent practicable, such assessments should provide central estimates of potential risks in conjunction with lower

and upper bounds (e.g., confidence limits) and a clear statement of the uncertainty associated with these estimates.

In the absence of sufficient data or understanding to develop of a robust, biologically based model, an appropriate policy choice is to have a single preferred curve-fitting model for each type of data set. Many different curve-fitting models have been developed, and those that fit the observed data reasonably well may lead to several-fold differences in estimated risk at the lower end of the observed range. In addition, goodness-of-fit to the experimental observations is not by itself an effective means of discriminating among models that adequately fit the data (OSTP, 1985). To provide some measure of consistency across different carcinogen assessments, EPA uses a standard curve-fitting procedure for tumor incidence data. Assessments that include a different approach should provide an adequate justification and compare their results with those from the standard procedure. Application of models to data should be conducted in an open and transparent manner.

1.3.2. Mode of Action

The use of mode of action[2] in the assessment of potential carcinogens is a main focus of these cancer guidelines. This area of emphasis arose because of the significant scientific advances that have developed concerning the causes of cancer induction. Elucidation of a mode of action for a particular cancer response in animals or humans is a data-rich determination. Significant information should be developed to ensure that a scientifically justifiable mode of action underlies the process leading to cancer at a given site. In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data:

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[2] The term *"mode of action"* is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A *"key event"* is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element. Mode of action is contrasted with "*mechanism of action*," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action. The toxicokinetic processes that lead to formation or distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode of action as the term is used here. There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.

animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity.

Understanding of mode of action can be a key to identifying processes that may cause chemical exposures to differentially affect a particular population segment or lifestage. Some modes of action are anticipated to be mutagenic and are assessed with a linear approach. This is the mode of action of radiation and several other agents that are known carcinogens. Other modes of action may be modeled with either linear or nonlinear[3] approaches after a rigorous analysis of available data under the guidance provided in the framework for mode of action analysis (see Section 2.4.3).

1.3.3. Weight of Evidence Narrative

The cancer guidelines emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This is accomplished in a single integrative step after assessing all of the individual lines of evidence, which is in contrast to the step-wise approach in the 1986 cancer guidelines. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiologic studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insights into the possible mode(s) of action and likelihood of human cancer hazard and risk. The cancer guidelines recognize the growing sophistication of research methods,

[3]The term "*nonlinear*" is used here in a narrower sense than its usual meaning in the field of mathematical modeling. In these cancer guidelines, the term "*nonlinear*" refers to threshold models (which show no response over a range of low doses that include zero) and some nonthreshold models (e.g., a quadractic model, which shows some response at all doses above zero). In these cancer guidelines, a nonlinear model is one whose slope is zero at (and perhaps above) a dose of zero. A *low-dose-linear* model is one whose slope is greater than zero at a dose of zero. A low-dose-linear model approximates a straight line only at very low doses; at higher doses near the observed data, a low-dose-linear model can display curvature. The term "*low-dose-linear*" is often abbreviated "linear," although a low-dose-linear model is not linear at all doses. Use of nonlinear approaches does not imply a biological threshold dose below which the response is zero. Estimating thresholds can be problematic; for example, a response that is not statistically significant can be consistent with a small risk that falls below an experiment's power of detection.

particularly in their ability to reveal the modes of action of carcinogenic agents at cellular and subcellular levels as well as toxicokinetic processes.

Weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed, to the extent that these are revealed in the toxicological and other biologically important features of the agent.

The weight of evidence narrative to characterize hazard summarizes the results of the hazard assessment and provides a conclusion with regard to human carcinogenic potential. The narrative explains the kinds of evidence available and how they fit together in drawing conclusions, and it points out significant issues/strengths/limitations of the data and conclusions. Because the narrative also summarizes the mode of action information, it sets the stage for the discussion of the rationale underlying a recommended approach to dose-response assessment.

In order to provide some measure of clarity and consistency in an otherwise free-form, narrative characterization, standard descriptors are used as part of the hazard narrative to express the conclusion regarding the weight of evidence for carcinogenic hazard potential. There are five recommended standard hazard descriptors: "*Carcinogenic to Humans*," "*Likely to Be Carcinogenic to Humans*," "*Suggestive Evidence of Carcinogenic Potential*," "*Inadequate Information to Assess Carcinogenic Potential*," and "*Not Likely to Be Carcinogenic to Humans*." Each standard descriptor may be applicable to a wide variety of data sets and weights of evidence and is presented only in the context of a weight of evidence narrative. Furthermore, as described in Section 2.5 of these cancer guidelines, more than one conclusion may be reached for an agent.

1.3.4. Dose-response Assessment

Dose-response assessment evaluates potential risks to humans at particular exposure levels. The approach to dose-response assessment for a particular agent is based on the conclusion reached as to its potential mode(s) of action for each tumor type. Because an agent may induce multiple tumor types, the dose-response assessment includes an analysis of all tumor types, followed by an overall synthesis that includes a characterization of the risk estimates across tumor types, the strength of the mode of action information of each tumor type, and the

anticipated relevance of each tumor type to humans, including susceptible populations and lifestages (e.g., childhood).

Dose-response assessment for each tumor type is performed in two steps: assessment of observed data to derive a point of departure (POD),[4] followed by extrapolation to lower exposures to the extent that is necessary. Data from epidemiologic studies, of sufficient quality, are generally preferred for estimating risks. When animal studies are the basis of the analysis, the estimation of a human-equivalent dose should utilize toxicokinetic data to inform cross-species dose scaling if appropriate and if adequate data are available. Otherwise, default procedures should be applied. For oral dose, based on current science, an appropriate default option is to scale daily applied doses experienced for a lifetime in proportion to body weight raised to the 3/4 power (U.S. EPA, 1992b). For inhalation dose, based on current science, an appropriate default methodology estimates respiratory deposition of particles and gases and estimates internal doses of gases with different absorption characteristics. When toxicokinetic modeling (see Section 3.1.2) is used without toxicodynamic modeling (see Section 3.2.2), the dose-response assessment develops and supports an approach for addressing toxicodynamic equivalence, perhaps by retaining some of the cross-species scaling factor (see Section 3.1.3). Guidance is also provided for adjustment of dose from adults to children (see Section 4.3.1).

Response data on effects of the agent on carcinogenic processes are analyzed (nontumor data) in addition to data on tumor incidence. If appropriate, the analyses of data on tumor incidence and on precursor effects may be used in combination. To the extent the relationship between precursor effects and tumor incidence are known, precursor data may be used to estimate a dose-response function below the observable tumor data. Study of the dose-response function for effects believed to be part of the carcinogenic process influenced by the agent may also assist in evaluating the relationship of exposure and response in the range of observation and at exposure levels below the range of observation.

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[4] A "*point of departure*" (POD) marks the beginning of extrapolation to lower doses. The POD is an estimated dose (usually expressed in human-equivalent terms) near the lower end of the observed range, without significant extrapolation to lower doses.

The first step of dose-response assessment is evaluation within the range of observation. Approaches to analysis of the range of observation of epidemiologic studies are determined by the type of study and how dose and response are measured in the study. In the absence of adequate human data for dose-response analysis, animal data are generally used. If there are sufficient quantitative data and adequate understanding of the carcinogenic process, a biologically based model may be developed to relate dose and response data on an agent-specific basis. Otherwise, as a default procedure, a standard model can be used to curve-fit the data.

The POD for extrapolating the relationship to environmental exposure levels of interest, when the latter are outside the range of observed data, is generally the lower 95% confidence limit on the lowest dose level that can be supported for modeling by the data. SAB (1997) suggested that, "it may be appropriate to emphasize lower statistical bounds in screening analyses and in activities designed to develop an appropriate human exposure value, since such activities require accounting for various types of uncertainties and a lower bound on the central estimate is a scientifically-based approach accounting for the uncertainty in the true value of the ED_{10} [or central estimate]." However, the consensus of the SAB (1997) was that, "both point estimates and statistical bounds can be useful in different circumstances, and recommended that the Agency routinely calculate and present the point estimate of the ED_{10} [or central estimate] and the corresponding upper and lower 95% statistical bounds." For example, it may be appropriate to emphasize the central estimate in activities that involve formal uncertainty analysis that are required by OMB Circular A-4 (OMB, 2003) as well as ranking agents as to their carcinogenic hazard. Thus, risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decisionmakers.

The second step of dose-response assessment is extrapolation to lower dose levels, if needed. This extrapolation is based on extension of a biologically based model if supported by substantial data (see Section 3.3.2). Otherwise, default approaches can be applied that are consistent with current understanding of mode(s) of action of the agent, including approaches that assume linearity or nonlinearity of the dose-response relationship, or both. A default approach for linearity extends a straight line from the POD to zero dose/zero response (see

Section 3.3.3). The linear approach is used when: (1) there is an absence of sufficient information on modes of action or (2) the mode of action information indicates that the dose-response curve at low dose is or is expected to be linear. Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration (see Section 3.3.4).

1.3.5. Susceptible Populations and Lifestages

An important use of mode of action information is to identify susceptible populations and lifestages. It is rare to have epidemiologic studies or animal bioassays conducted in susceptible individuals. This information need can be filled by identifying the key events of the mode of action and then identifying risk factors, such as differences due to genetic polymorphisms, disease, altered organ function, lifestyle, and lifestage, that can augment these key events. To do this, the information about the key precursor events is reviewed to identify particular populations or lifestages that can be particularly susceptible to their occurrence (see Section 2.4.3.4). Any information suggesting quantitative differences between populations or lifestages is flagged for consideration in the dose-response assessment (see Section 3.5 and U.S. EPA 2002b).

1.3.6. Evaluating Risks from Childhood Exposures

NRC (1994) recommended that "EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults." Executive Order 13045 (1997) requires that "each Federal Agency shall make it a high priority to identify and assess environmental health and safety risks that may disproportionately affect children, and shall ensure that their policies, programs, and standards address disproportionate risks that result from environmental health risks or safety risks." In assessing risks to children, EPA considers both effects manifest during childhood and early-life exposures that can contribute to effects at any time later in life.

These cancer guidelines view childhood as a sequence of lifestages rather than viewing children as a subpopulation, the distinction being that a subpopulation refers to a portion of the

population, whereas a lifestage is inclusive of the entire population. Exposures that are of concern extend from conception through adolescence and also include pre-conception exposures of both parents. These cancer guidelines use the term "childhood" in this more inclusive sense.

Rarely are there studies that directly evaluate risks following early-life exposure. Epidemiologic studies of early-life exposure to environmental agents are seldom available. Standard animal bioassays generally begin dosing after the animals are several weeks old, when many organ systems are mature. This could lead to an understatement of risk, because an accepted concept in the science of carcinogenesis is that young animals are usually more susceptible to the carcinogenic activity of a chemical than are mature animals (McConnell, 1992).

At this time, there is some evidence of higher cancer risks following early-life exposure. For radiation carcinogenesis, data indicate that risks for several forms of cancer are highest following childhood exposure (NRC, 1990; Miller, 1995; U.S. EPA, 1999c). These human results are supported by the few animal bioassays that include perinatal (prenatal or early postnatal) exposure. Perinatal exposure to some agents can induce higher incidences of the tumors seen in standard bioassays; some examples include vinyl chloride (Maltoni et al., 1981), diethylnitrosamine (Peto et al., 1984), benzidine, DDT, dieldrin, and safrole (Vesselinovitch et al., 1979). Moreover, perinatal exposure to some agents, including vinyl chloride (Maltoni et al., 1981) and saccharin (Cohen, 1995; Whysner and Williams, 1996), can induce different tumors that are not seen in standard bioassays. Surveys comparing perinatal carcinogenesis bioassays with standard bioassays for a limited number of chemicals (McConnell, 1992; U.S. EPA, 1996b) have concluded that

- the same tumor sites are usually observed following either perinatal or adult exposure, and

- perinatal exposure in conjunction with adult exposure usually increases the incidence of tumors or reduces the latent period before tumors are observed.

The risk attributable to early-life exposure often appears modest compared with the risk from lifetime exposure, but it can be about 10-fold higher than the risk from an exposure of similar duration occurring later in life (Ginsberg, 2003). Further research is warranted to investigate the extent to which these findings apply to specific agents, chemical classes, and modes of action or in general.

These empirical results are consistent with current understanding of the biological processes involved in carcinogenesis, which leads to a reasonable expectation that children can be more susceptible to many carcinogenic agents (Anderson et al., 2000; Birnbaum and Fenton, 2003; Ginsberg, 2003; Miller et al., 2002; Scheuplein et al., 2002). Some aspects potentially leading to childhood susceptibility are listed below.

- Differences in the capacity to metabolize and clear chemicals can result in larger or smaller internal doses of the active agent(s).

- More frequent cell division during development can result in enhanced expression of mutations due to the reduced time available for repair of DNA lesions (Slikker et al., 2004).

- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.

- More frequent cell division during development can result in clonal expansion of cells with mutations from prior unrepaired DNA damage (Slikker et al., 2004).

- Some components of the immune system are not fully functional during development (Holladay and Smialowicz, 2000; Holsapple et al., 2003).

- Hormonal systems operate at different levels during different lifestages.

- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life (Anderson et al., 2000; Birnbaum and Fenton, 2003; Fenton and Davis, 2002).

To evaluate risks from early-life exposure, these cancer guidelines emphasize the role of toxicokinetic information to estimate levels of the active agent in children and toxicodynamic information to identify whether any key events of the mode of action are of increased concern early in life. Developmental toxicity studies can provide information on critical periods of exposure for particular targets of toxicity.

An approach to assessing risks from early-life exposure is presented in Figure 1-1. In the hazard assessment, when there are mode of action data, the assessment considers whether these data have special relevance during childhood, considering the various aspects of development listed above. Examples of such data include toxicokinetics that predict a sufficiently large internal dose in children or a mode of action where a key precursor event is more likely to occur during childhood. There is no recommended default to settle the question of whether tumors arising through a mode of action are relevant during childhood; and adequate understanding the mode of action implies that there are sufficient data (on either the specific agent or the general mode of action) to form a confident conclusion about relevance during childhood (see Section 2.4.3.4).

In the dose-response assessment, the potential for susceptibility during childhood warrants explicit consideration in each assessment. These cancer guidelines encourage developing separate risk estimates for children according to a tiered approach that considers what pertinent data are available (see Section 3.5). Childhood may be a susceptible period; moreover, exposures during childhood generally are not equivalent to exposures at other times and may be treated differently from exposures occurring later in life (see Section 3.5). In addition, adjustment of unit risk estimates may be warranted when used to estimate risks from childhood exposure (see Section 4.4).

At this time, several limitations preclude a full assessment of children's risk. There are no generally used testing protocols to identify potential environmental causes of cancers that are

unique to children, including several forms of childhood cancer and cancers that develop from parental exposures, and cases where developmental exposure may alter susceptibility to carcinogen exposure in the adult (Birnbaum and Fenton, 2003). Dose-response assessment is limited by an inability to observe how developmental exposure can modify incidence and latency and an inability to estimate the ultimate tumor response resulting from induced susceptibility to later carcinogen exposures.

To partially address the limitations identified above, EPA developed in conjunction with these cancer guidelines, *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ("Supplemental Guidance"). The Supplemental Guidance addresses a number of issues pertaining to cancer risks associated with early-life exposures generally, but provides specific guidance on procedures for adjusting cancer potency estimates only for carcinogens acting through a mutagenic mode of action. This Supplemental Guidance recommends, for such chemicals when no chemical-specific data exist, a default approach using estimates from chronic studies (i.e., cancer slope factors) with appropriate modifications to address the potential for differential risk of early-lifestage exposure.

The Agency considered both the advantages and disadvantages to extending the recommended, age dependent adjustment factors for carcinogenic potency to carcinogenic agents for which the mode of action remains unknown. EPA decided to recommend these factors only for carcinogens acting through a mutagenic mode of action based on a combination of analysis of available data and long-standing science policy positions which govern the Agency's overall approach to carcinogen risk assessment. In general, the Agency prefers to rely on analyses of data, rather than general defaults. When data are available for a sensitive lifestage, they would be used directly to evaluate risks for that chemical and that lifestage on a case-by-case basis. In the case of nonmutagenic carcinogens, when the mode of action is unknown, the data were judged by EPA to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. In this situation, a linear low-dose extrapolation methodology (without further adjustment) is recommended. It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach

provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life sensitivity or when the mode of action is not mutagenic.

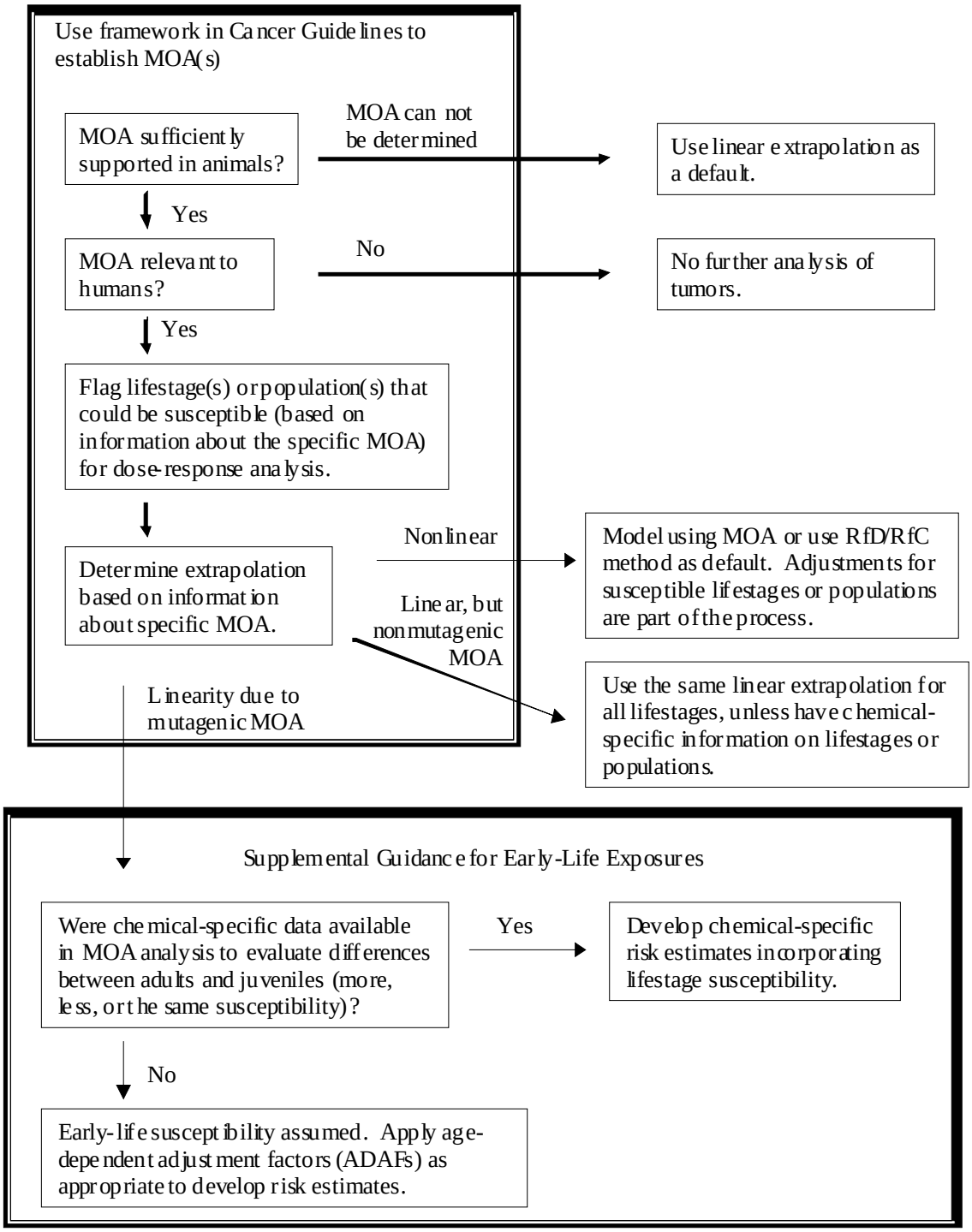
The Agency expects to produce additional supplemental guidance for other modes of action, as data from new research and toxicity testing indicate it is warranted. EPA intends to focus its research, and work collaboratively with its federal partners, to improve understanding of the implications of early life exposure to carcinogens. Development of guidance for estrogenic agents and chemicals acting through other processes resulting in endocrine disruption and subsequent carcinogenesis, for example, might be a reasonable priority in light of the human experience with diethylstilbesterol and the existing early life animal studies. It is worth noting that each mode of action for endocrine disruption will probably require separate analysis.

As the Agency examines additional carcinogenic agents, the age groupings may differ from those recommended for assessing cancer risks from early-life exposure to chemicals with a mutagenic mode of action. Puberty and its associated biological changes, for example, involve many biological processes that could lead to changes in sensitivity to the effects of some carcinogens, depending on their mode of action. The Agency is interested in identifying lifestages that may be particularly sensitive or refractory for carcinogenesis, and believes that the mode of action framework described in these cancer guidelines is an appropriate mechanism for elucidating these lifestages. For each additional mode of action evaluated, the various age groupings determined to be at differential risk may differ from those proposed in the Supplemental Guidance. For example, the age groupings selected for the age-dependent adjustments for carcinogens acting through a mutagenic mode of action were initially selected based on the available data, i.e., for the laboratory animal age range representative of birth to < 2 years in humans. More limited data and information on human biology were used to determine a science-informed policy regarding 2 to < 16 years. Data were not available to refine the latter age group. If more data become available regarding carcinogens with a mutagenic mode of action, consideration may be given to further refinement of these age groups.

1.3.7. Emphasis on Characterization

The cancer guidelines emphasize the importance of a clear and useful characterization narrative that summarizes the analyses of hazard, dose-response, and exposure assessment. These characterizations summarize the assessments to explain the extent and weight of evidence, major points of interpretation and rationale for their selection, strengths and weaknesses of the evidence and the analysis, and discuss alternative conclusions and uncertainties that deserve serious consideration (U.S. EPA, 2000b). They serve as starting materials for the overall risk characterization process that completes the risk assessment.

Figure 1-1. Flow chart for early-life risk assessment using mode of action framework.



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